CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074613

Trade Name : BUMETANIDE INJECTION USP

Generic Name: Bumetanide Injection USP, 0.25mg/ml

Sponsor : Gensia Laboratories, Ltd.

Approval Date: November 18, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074613

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074613

APPROVAL LETTER

ANDA 74-613

NOV 18 1997

Gensia Laboratories, LTD.
Attention: Donald J. Harrigan
19 Hughes
Irvine, CA 92718-1902

Dear Sir:

This is in reference to your abbreviated new drug application dated January 20, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Bumetanide Injection USP, 0.25 mg/mL.

Reference is also made to your amendments dated April 26, August 23, and October 27, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined that your Bumetanide Injection USP, 0.25 mg/mL, is bioequivalent and, therefore, therapeutically equivalent to the listed drug (Bumex® Injection, 0.25 mg/mL, of Hoffmann LaRoche, Inc.).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

11-18-97

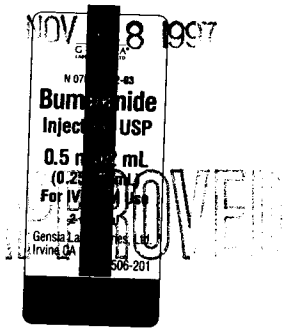
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074613

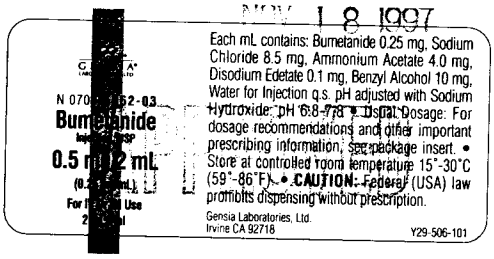
FINAL PRINTED LABELING

Container Label NDC 0703-5062-03
(Part No. Y29-506-201)

0.5 mg/2 mL, 2 mL fill in a 2 mL vial



Shelf Pack "A" Label NDC 0703-5062-03
(Part No. Y29-506-101)



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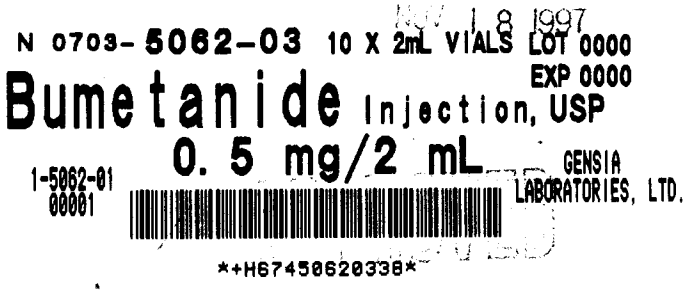
(Part No. 1-5062-01)



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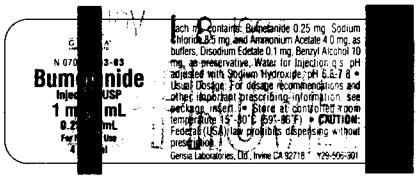
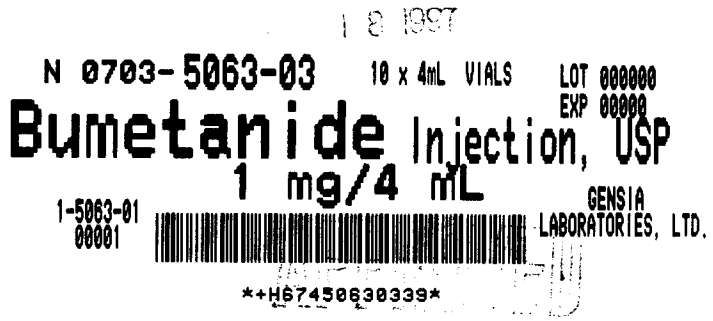
(Part No. Y29-506-301)

1 mg/4 mL, 4 mL fill in a 5 mL vial



Shelf Pack "B" Label NDC 0703-5063-03
(Part No. 1-5063-01)



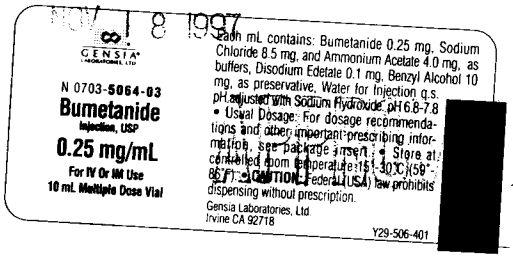
Mango

Telephone Amendment - Minor

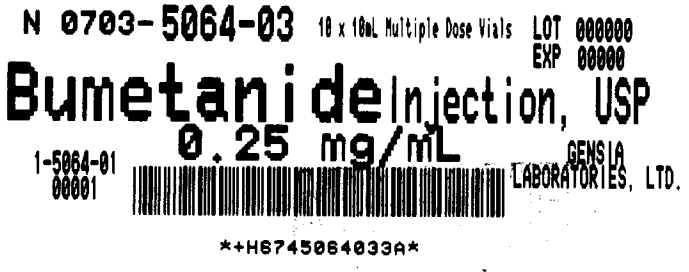
Gensia Laboratories, Ltd.
Bumetanide Injection, USP
ANDA 74-613

Container/Shelf Pack "A" Label NDC 0703-5064-03
(Part No. Y29-506-401)

2.5 mg/10 mL, 10 mL fill in a 10 mL vial



Shelf Pack "B" Label NDC 0703-5064-03
(Part No. 1-5064-01)



Y36-109-201
Package Insert

GENSIA®
LABORATORIES, LTD.

Bumetanide Injection, USP

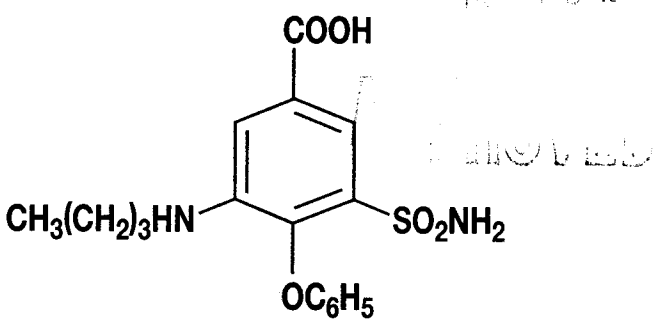
WARNING: Bumetanide is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dosage schedule have to be adjusted to the individual patient's needs. (See **DOSAGE AND ADMINISTRATION**.)

DESCRIPTION

Bumetanide is a loop diuretic, available as 2 mL vials, 4 mL vials and 10 mL vials (0.25 mg/mL) for intravenous or intramuscular injection as a sterile solution.

Each mL contains: Bumetanide 0.25 mg, Sodium Chloride 8.5 mg and Ammonium Acetate 4.0 mg as buffers, Disodium Edetate 0.1 mg, Benzyl Alcohol 10 mg as preservative, Water for Injection q.s. pH adjusted with Sodium Hydroxide. pH 6.8-7.8

Chemically, bumetanide is 3-(butylamino)-4-phenoxy-5-sulfamoylbenzoic acid. It is a practically white powder, slightly soluble in water; soluble in alkaline solutions, having the following structural formula:



$C_{17}H_{20}N_2O_5S$ 364.42

CLINICAL PHARMACOLOGY

Bumetanide is a loop diuretic with a rapid onset and short duration of action. Pharmacological and clinical studies have shown that 1 mg Bumetanide has a diuretic potency equivalent to approximately 40 mg furosemide. The major site of Bumetanide action is the ascending limb of the loop of Henle.

The mode of action has been determined through various clearance studies in both humans and experimental animals. Bumetanide inhibits sodium reabsorption in the ascending limb of the loop of Henle, as shown by marked reduction of free-water clearance (CH_2O) during hydration and tubular free-water reabsorption (T^CH_2O) during hydropenia. Reabsorption of chloride in the ascending limb is also blocked by Bumetanide, and Bumetanide is somewhat more chloruretic than natriuretic.

Potassium excretion is also increased by Bumetanide, in a dose-related fashion.

Bumetanide may have an additional action in the proximal tubule. Since phosphate reabsorption takes place largely in the proximal tubule, phosphaturia during Bumetanide-induced diuresis is indicative of this additional action. This is further supported by the reduction in the renal clearance of Bumetanide by probenecid, associated with diminution in the natriuretic response. This proximal tubular activity does not seem to be related to an inhibition of carbonic anhydrase. Bumetanide does not appear to have a noticeable action on the distal tubule.

Bumetanide decreases uric acid excretion and increases serum uric acid. Diuresis starts within minutes following an intravenous injection and reaches maximum levels within 15 to 30 minutes.

Several pharmacokinetic studies have shown that Bumetanide, administered orally or parenterally, is eliminated rapidly in humans, with a half-life of between 1 and 1 1/2 hours. Plasma protein-binding is in the range of 94% to 96%.

ıl administration of carbon-14 labeled Bumetanide to human volunteers revealed that .% of the administered radioactivity was excreted in the urine, 45% of it as unchanged drug. Urinary and biliary metabolites identified in this study were formed by oxidation of the N-butyl side chain. Biliary excretion of Bumetanide amounted to only 2% of the administered dose.

INDICATIONS AND USAGE

Bumetanide injection is indicated for the treatment of edema associated with congestive heart failure, hepatic and renal disease, including the nephrotic syndrome.

Almost equal diuretic response occurs after oral and parenteral administration of Bumetanide. Therefore, if impaired gastrointestinal absorption is suspected or oral administration is not practical, Bumetanide should be given by the intramuscular or intravenous route.

Successful treatment with Bumetanide following instances of allergic reactions to furosemide suggests a lack of cross-sensitivity.

CONTRAINDICATIONS

Bumetanide is contraindicated in anuria. Although Bumetanide can be used to induce diuresis in renal insufficiency, any marked increase in blood urea nitrogen or creatinine, or the development of oliguria during therapy of patients with progressive renal disease, is an indication for discontinuation of treatment with Bumetanide. Bumetanide is also contraindicated in patients in hepatic coma or in states of severe electrolyte depletion until the condition is improved or corrected. Bumetanide is contraindicated in patients hypersensitive to this drug.

WARNINGS

1. Volume and electrolyte depletion. The dose of Bumetanide should be adjusted to the patient's need. Excessive doses or too frequent administration can lead to profound water loss, electrolyte depletion, dehydration, reduction in blood volume and circulatory collapse with the possibility of vascular thrombosis and embolism, particularly in elderly patients.

2. Hypokalemia. Hypokalemia can occur as a consequence of Bumetanide administration. Prevention of hypokalemia requires particular attention in the following conditions: patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis and ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, certain diarrheal states, or other states where hypokalemia is thought to represent particular added risks to the patient, i.e., history of ventricular arrhythmias.

In patients with hepatic cirrhosis and ascites, sudden alterations of electrolyte balance may precipitate hepatic encephalopathy and coma. Treatment in such patients is best initiated in the hospital with small doses and careful monitoring of the patient's clinical status and electrolyte balance. Supplemental potassium and/or spironolactone may prevent hypokalemia and metabolic alkalosis in these patients.

3. Ototoxicity. In cats, dogs and guinea pigs, Bumetanide has been shown to produce ototoxicity. In these test animals Bumetanide was 5 to 6 times more potent than furosemide and, since the diuretic potency of Bumetanide is about 40 to 60 times furosemide, it is anticipated that blood levels necessary to produce ototoxicity will rarely be achieved. The potential exists, however, and must be considered a risk of intravenous therapy, especially at high doses, repeated frequently in the face of renal excretory function impairment. Potentiation of aminoglycoside ototoxicity has not been tested for Bumetanide. Like other members of this class of diuretics, Bumetanide probably shares this risk.

4. Allergy to sulfonamides. Patients allergic to sulfonamides may show hypersensitivity to Bumetanide.

5. Thrombocytopenia. Since there have been rare spontaneous reports of thrombocytopenia from postmarketing experience, patients should be observed regularly for possible occurrence of thrombocytopenia.

PRECAUTIONS

General: Serum potassium should be measured periodically and potassium supplements or potassium-sparing diuretics added if necessary. Periodic determinations of other electrolytes are advised in patients treated with high doses or for prolonged periods, particularly in those on low salt diets.

Hyperuricemia may occur; it has been asymptomatic in cases reported to date. Reversible elevations of the BUN and creatinine may also occur, especially in association with dehydration and particularly in patients with renal insufficiency. Bumetanide may increase urinary calcium excretion with resultant hypocalcemia.

Diuretics have been shown to increase the urinary excretions of magnesium; this may result in hypomagnesemia.

Laboratory Tests: Studies in normal subjects receiving Bumetanide revealed no adverse effects on glucose tolerance, plasma insulin, glucagon and growth hormone levels, but the possibility of an effect on glucose metabolism exists. Periodic determinations of blood sugar should be done, particularly in patients with diabetes or suspected latent diabetes.

Patients under treatment should be observed regularly for possible occurrence of blood dyscrasias, liver damage or idiosyncratic reactions, which have been reported occasionally in foreign marketing experience. The relationship of these occurrences to Bumetanide use is not certain.

Drug Interactions

1. Drugs with ototoxic potential (see **WARNINGS**): Especially in the presence of impaired renal function, the use of parenterally administered Bumetanide in patients to whom aminoglycoside antibiotics are also being given should be avoided except, in life-threatening conditions.

2. Drugs with nephrotoxic potential: There has been no experience on the concurrent use of Bumetanide with drugs known to have nephrotoxic potential. Therefore, the simultaneous administration of these drugs should be avoided.

3. Lithium: Lithium should generally not be given with diuretics (such as Bumetanide) because they reduce its renal clearance and add a high risk of lithium toxicity.

4. Probenecid: Pretreatment with probenecid reduces both the natriuresis and hyperreninemia produced by Bumetanide. This antagonistic effect of probenecid on Bumetanide natriuresis is not due to a direct action on sodium excretion but is probably secondary to its inhibitory effect on renal tubular secretion of bumetanide. Thus, probenecid should not be administered concurrently with Bumetanide.

5. Indomethacin: Indomethacin blunts the increases in urine volume and sodium excretion seen during Bumetanide treatment and inhibits the bumetanide-induced increase in plasma renin activity. Concurrent therapy with Bumetanide is thus not recommended.

6. Antihypertensives: Bumetanide may potentiate the effect of various antihypertensive drugs, necessitating a reduction in the dosage of these drugs.

7. Digoxin: Interaction studies in humans have shown no effect on digoxin blood levels.

8. Anticoagulants: Interaction studies in humans have shown Bumetanide to have no effect on warfarin metabolism or on plasma prothrombin activity.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Bumetanide was devoid of mutagenic activity in various strains of *Salmonella typhimurium* when tested in the presence or absence of an *in vitro* metabolic activation system. An 18-month study showed an increase in mammary adenomas of questionable significance in female rats receiving oral doses of 60 mg/kg/day (2000 times a 2 mg human dose). A repeat study at the same doses failed to duplicate this finding.

Reproduction studies were performed to evaluate general reproductive performance and fertility in rats at oral dose levels of 10, 30, 60 or 100 mg/kg/day. The pregnancy rate was slightly decreased in the treated animals; however, the differences were small and not statistically significant.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Bumetanide is neither teratogenic nor embryocidal in mice when given in doses up to 3400 times the maximum human therapeutic dose.

Bumetanide has been shown to be nonteratogenic, but it has a slight embryocidal effect in rats when given in doses of 3400 times the maximum human therapeutic dose and in rabbits at doses of 3.4 times maximum human therapeutic dose. In one study, moderate growth retardation and increased incidence of delayed ossification of sternebrae were observed in rats at oral doses of 100 mg/kg/day, 3400 times the maximum human therapeutic dose. These effects were associated with maternal weight reductions noted during dosing. No such adverse effects were observed at 30 mg/kg/day (1000 times the maximum human therapeutic dose). No fetotoxicity was observed at 1000 to 2000 times the human therapeutic dose.

In rabbits, a dose-related decrease in litter size and an increase in resorption rate were noted at oral doses of 0.1 and 0.3 mg/kg/day (3.4 and 10 times the maximum human therapeutic dose). A slightly increased incidence of delayed ossification of sternebrae occurred at 0.3 mg/kg/day; however, no such adverse effects were observed at the dose of 0.03 mg/kg/day. The sensitivity of the rabbit to Bumetanide parallels the marked pharmacologic and toxicologic effects of the drug in this species.

Bumetanide was not teratogenic in the hamster at an oral dose of 0.5 mg/kg/day (17 times the maximum human therapeutic dose). Bumetanide was not teratogenic when given intravenously to mice and rats at doses up to 140 times the maximum human therapeutic dose.

There are no adequate and well-controlled studies in pregnant women. A small investigational experience in the United States and marketing experience in other countries to date have not indicated any evidence of adverse effects on the fetus, but these data do not rule out the possibility of harmful effects. Bumetanide should be given to a pregnant woman only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. As a general rule, nursing should not be undertaken while the patient is on Bumetanide since it may be excreted in human milk.

Pediatric Use: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS

The most frequent clinical adverse reactions considered probably or possibly related to Bumetanide are muscle cramps (seen in 1.1% of treated patients), dizziness (1.1%), hypotension (0.8%), headache (0.6%), nausea (0.6%), and encephalopathy (in patients with preexisting liver disease) (0.6%). One or more of these adverse reactions have been reported in approximately 4.1% of Bumetanide-treated patients.

Less frequent clinical adverse reactions to Bumetanide are impaired hearing (0.5%), pruritus (0.4%), electrocardiogram changes (0.4%), weakness (0.2%), hives (0.2%), abdominal pain (0.2%), arthritic pain (0.2%), musculoskeletal pain (0.2%), rash (0.2%) and vomiting (0.2%). One or more of these adverse reactions have been reported in approximately 2.9% of Bumetanide-treated patients.

Other clinical adverse reactions, which have each occurred in approximately 0.1% of patients, are vertigo, chest pain, ear discomfort, fatigue, dehydration, sweating, hyperventilation, dry mouth, upset stomach, renal failure, asterixis, itching, nipple tenderness, diarrhea, premature ejaculation and difficulty maintaining an erection.

Laboratory abnormalities reported have included hyperuricemia (in 18.4% of patients tested), hypochloremia (14.9%), hypokalemia (14.7%), azotemia (10.6%), hyponatremia (9.2%), increased serum creatinine (7.4%), hyperglycemia (6.6%), and variations in phosphorus (4.5%), CO_2 content (4.3%), bicarbonate (3.1%) and calcium (2.4%). Although manifestations of the pharmacologic action of Bumetanide, these conditions may become pronounced by intensive therapy.

Also reported have been thrombocytopenia (0.2%) and deviations in hemoglobin (0.8%), prothrombin time (0.8%), hematocrit (0.6%), WBC (0.3%) and differential counts (0.1%). There have been rare spontaneous reports of thrombocytopenia from postmarketing experience.

Diuresis induced by Bumetanide may also rarely be accompanied by changes in LDH (1.0%), total serum bilirubin (0.8%), serum proteins (0.7%), SGOT (0.6%), SGPT (0.5%), alkaline phosphatase (0.4%), cholesterol (0.4%) and creatinine clearance (0.3%). Increases in urinary glucose (0.7%) and urinary protein (0.3%) have also been seen.

OVERDOSAGE

Overdosage can lead to acute profound water loss, volume and electrolyte depletion, dehydration, reduction of blood volume and circulatory collapse with a possibility of vascular thrombosis and embolism. Electrolyte depletion may be manifested by weakness, dizziness, mental confusion, anorexia, lethargy, vomiting and cramps. Treatment consists of replacement of fluid and electrolyte losses by careful monitoring of the urine and electrolyte output and serum electrolyte levels.

DOSAGE AND ADMINISTRATION

Dosage should be individualized with careful monitoring of patient response.

Parenteral Administration: Bumetanide injection may be administered parenterally (IV or IM) to patients in whom gastrointestinal absorption may be impaired or in whom oral administration is not practical.

Parenteral treatment should be terminated and oral treatment instituted as soon as possi.

The usual initial dose is 0.5 to 1 mg intravenously or intramuscularly. Intravenous administration should be given over a period of 1 to 2 minutes. If the response to an initial dose is deemed insufficient, a second or third dose may be given at intervals of 2 to 3 hours, but should not exceed a daily dosage of 10 mg.

Miscibility and Parenteral Solutions: The compatibility tests of Bumetanide injection (0.25 mg/mL, 2 mL vials) with Dextrose Injection 5%, and Sodium Chloride 0.9%, and lactated Ringer's solution in both glass and plasticized PVC (Viaflex) containers have shown no significant absorption effect with either containers, nor a measurable loss of potency due to degradation of the drug. However, solutions should be freshly prepared and used within 24 hours.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED

Bumetanide Injection, USP 0.25 mg/mL is supplied in amber vials as follows:

NDC Number	Size
0703-5062-03	2 mL
0703-5063-03	4 mL
0703-5064-03	10 mL Multiple Dose Vial

Packaged 10 per shelf pack.

Store at controlled room temperature 15° - 30° C (59° - 86° F).

CAUTION: Federal (USA) law prohibits dispensing without prescription.

Issued: April 1996

Gensia Laboratories, Ltd.
Irvine CA 92718

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074613

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO 3

2. ANDA 74-613

3. NAME AND ADDRESS OF APPLICANT
Gensia Laboratories
Attention: Donald J. Harrigan
19 Hughes
Irvine, CA 92718-1902
714-455-4700

4. LEGAL BASIS FOR SUBMISSION: patent expired

5. SUPPLEMENT(s) NA

6. PROPRIETARY NAME NA
Roche Bumex^{R}

7. NONPROPRIETARY NAME
Bumetanide, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
NA

9. AMENDMENTS AND OTHER DATES:
FDA: 8/16/96 NA letter issued.

Firm:
Orig.submitted 1/20/95
New corr.submitted 8/23/96
Amendment submitted 10/27/97

10. PHARMACOLOGICAL CATEGORY diuretic

11. Rx

12. RELATED IND/NDA/DMF(s) see # 37

13. DOSAGE FORM
IV/Im injectable
2 mL
4 mL
10 mL

14. POTENCY
0.25 mg/mL
0.50 mg
1 mg
2.5 mg

16. RECORDS AND REPORTS NA

18. CONCLUSIONS AND RECOMMENDATIONS:
Approval

19. REVIEWER:
J.Fan

DATE COMPLETED:

cc: ANDA 74-613
DUP File
Division File

Endorsements:
HFD-623/J.Fan/11-4-9[redacted](b)4 - Confidential[redacted] 11/5/97.
HFD-623/V.Sayeed, Ph[redacted]
X:\NEW\FIRMSAM\GENSIA\LTRS&REV\74613N3.D
F/T by: bc/11-4-97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074613

BIOEQUIVALENCE REVIEW(S)

JUL 20 1995

Bumetanide Injection, USP
0.25 mg/mL; 2, 4 and 10 mL/vial
ANDA # **74-613**
Reviewer: Z.Z. Wahba
WP #74613w.195

Gensia Laboratories, LTD
Irvine, CA
Submission Date:
Jan. 20, 1995

Review of a Waiver Request

I. BACKGROUND

1. The firm has requested that the in-vivo bioequivalence requirements for its product be waived under the provisions of 21 CFR 320.22(b)(1).

2. The reference product is Bumex® 0.25 mg/mL, manufactured by Roche Laboratories.

3. The drug product is intended for IM or IV administration.

4. Bumetanide is a loop diuretic with a rapid onset and short duration of action. It is indicated for the treatment of edema associated with congestive heart failure, hepatic and renal disease, including the nephrotic syndrome.

II. FORMULATION COMPARISON

Ingredients:	Test Product mg/mL	Ref. Product mg/mL
Bumetanide, USP	0.25	0.25
Sodium Chloride, USP	8.5	8.5
Ammonium Acetate	4.0	4.0
Disodium Edetate,USP	0.10	0.10
Benzyl Alcohol, NF	10.0	10.0
Water for injection,USP	q.s. to 1.0mL	q.s. to 1.0mL
Sodium Hydroxide, NF	pH adjustment to approximately 7	

COMMENTS

1. The waiver of in vivo bioequivalence study requirements should be granted based on 21 CFR section 320.22(b)(1).

   i. The drug product is a parenteral solution intended solely for administration by injection.

   ii. The drug product contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application.

III. RECOMMENDATION

The Division of Bioequivalence agrees that the information submitted by Gensia Laboratories, LTD demonstrates that Bumetanide Injection, USP, 0.25 mg/mL falls under 21 CFR Section 320.22(b)(1) of the Bioavailability/Bioequivalence Regulations. The waiver of the in vivo bioequivalence study for the 0.25 mg/mL injection of the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulation to be bioequivalent to Bumex®, 0.25 mg/ml, manufactured by Roche Laboratories.

The firm should be informed of the recommendation.

/S/

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE /S/ 7/17/95
FT INITIALED RMHATRE

Concur: /S/ Date: 7/20/95

Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

cc: ANDA 74-613 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Wahba), Drug File, Division File

ZZW/061695/071195/file #74613W.195